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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/932,546	POSPISILIK ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Response to election of species requirement filed 10/30/2003 is acknowledged. Applicant canceled claims 2-6, 9,10. Therefore, the election of species requirement is moot.

Claims pending are 1,7,8.

Specification

2. Specification is objected for the following reasons: The last paragraph on p. 13 is an orphan paragraph unrelated to Example 5 it follows. Further, Example 5 (p. 12, line 27) refers to Fig. 4 which does not present any data related to changes in blood pressure.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 1,7,8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn, in part, to use of inhibitors of "enzymes having DP IV-like enzymatic activity". The metes and bounds of the enzymes encompassed by the term "enzymes having DP IV-like

enzymatic activity" is not clear - what kind of activity constitutes DP IV-like enzymatic activity? Consequently, the scope of inhibitors to be used in the claim is not clear.

Claim Rejections - 35 USC § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1,7,8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are directed to reduction of both post-prandial hyperglycemia and blood pressure. Specification indicates that the genus of "elevated glucose levels" can result from various reasons, post-prandial hyperglycemia being just one of them (see, e.g., p. 7, bottom). Nowhere however, there is a disclosure of a particular embodiment of lowering, specifically, post-prandial hyperglycemia along with reduction in blood pressure. The only example related to reduction of blood pressure is effect of chronic administration of thiazolidine (Example 5); there is no demonstration of reduction of post-prandial hyperglycemia during such administration.

5. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 8 introduces new matter as it is directed to lowering blood pressure in mammals experiencing particular range, over 150 mm Hg, of blood pressure. Such limitation is not disclosed in specification as claimed.

6. Claims 1,7,8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing blood pressure in diabetic rats using thiazolidine fumarate, does not reasonably provide enablement for combined effect of lowering post-prandial hyperglycemia along with reduction in blood pressure. The only example related to reduction of blood pressure is effect of chronic administration of thiazolidine (Example 5); there is no demonstration of reduction of post-prandial hyperglycemia during such administration. There is no examples of the combined effect for any other inhibitor. Further, there is no guidance regarding the "effective amount" of the inhibitor to achieve the combined effect; the only general range described in the specification (p. 9) is related to reduction of glucose level rather than reduction in blood pressure level.

7. Claims 1,7,8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing blood pressure in diabetic rats using thiazolidine fumarate, does not reasonably provide enablement for decreasing blood pressure by any other DP-IV inhibitors. The only example in specification, Example 5, demonstrates effect of thiazolidine fumarate. Thiazolidines themselves

have multiple mechanisms of action (e.g., as chymase or Na/H exchanger inhibitors) so that it is not evident that in the observed effect of lowering blood pressure in diabetic rats thiazolidine fumarate acts as DP IV inhibitor. There is no demonstrated effect for any other DP-IV inhibitors, and there is no guidance regarding the "effective amount" of DP IV inhibitor - the only dosage range provided, in grams/kg, is for thiazolidines.

8. Claims 1,7,8 are rejected under 35 U.S.C. 112, first paragraph, because the specification,while being enabling for decreasing blood pressure in diabetic rats using thiazolidine fumarate, does not reasonably provide for decreasing blood pressure elevation caused by any other mechanisms. The claims are drawn to lowering blood pressure in general. The specification addresses only lowering of blood pressure concurrent with lowering blood glucose level. The only working example demonstrates lowering of blood pressure by thiazolidine fumarate in diabetic rats.

First, the art is unpredictable about correlation of blood pressure and glucose levels. Thus, Voors et al demonstrates than such correlation exists in some but not all populations (Database Medline, DN 7211820). Second, in regard to the effect of DP IV inhibitors on blood pressure, the art is also unpredictable. DP IV inhibition would result in increasing level of agents that would be expected to either act variably or increase, rather than decrease blood pressure. Thus, DP IV inhibition will result in increase of the level of incretins which will cause increase in blood pressure either directly or via increase in insulin level. See,e.g., Yamamoto et al (Database Caplus, DN 137:211177). Further, DP IV inhibition will result in increase of the level of substance P (Heymann et al; IDS filed 12/12/2001, reference CR),

which, depending on conditions, may cause either increase or decrease of the blood pressure (see, e.g., references of Hecht et al, Hancock et al., Brattstorm et al). Therefore, even for the DP IV-related events, the effect on blood pressure is unpredictable. In addition, for blood pressure elevated due to DP IV- unrelated events, the effect on blood pressure is even less expected and/or predictable.

9. Claims 1,7,8 are rejected under 35 U.S.C. 112, first paragraph, because the specification,while being enabling for decreasing blood pressure in diabetic rats using thiazolidine fumarate, does not reasonably provide enablement for treatment of any other mammals. The claims are directed to method of lowering blood pressure in mammals. The only example present in specification is for decreasing blood pressure in diabetic rats using thiazolidine fumarate. There are no examples demonstrating effect on other mammals, nor is the diabetic rat model is representative model for other mammals. As follows from the discussion in the previous rejection, art is unpredictable in regard to the effect of inhibition of DP IV on blood pressure.

Claim Rejections - 35 USC § 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States...

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1,7,8 are rejected under 35 U.S.C.103(a) as obvious over Mentlein et al. (reference CBK, IDS filed 05/12/2003) alone or in combination with Deacon et al (reference CV, IDS filed 05/12/2003), and further in view of Barbagallo et al(Database MEDLINE; PubMed ID: 8141167. American Journal of the medical sciences, (1994 Feb) 307 Suppl 1 S60-5)

The instant claims are drawn to method for lowering elevated blood glucose and elevated blood pressure by administering an inhibitor of Dipeptidyl Peptidase (DP IV).

It is well known that increase of insulin release is the reaction geared towards elimination of elevation in glucose level (see, e.g., Background section). Decrease in insulin release would hamper ability of an organism to eliminate the increase in glucose level and result in hyperglycemia. Further, it is known that elevated level of glucose may trigger elevation in blood pressure (see, e.g., Barbagallo et al).

Mentlein et al. teach that GIP_{1-42} and $GLP\text{-}1_{7-36}$ are hormones (called incretins) which potentiate glucose-induced insulin secretion, and that DP-IV initiates metabolism of these hormones. Because the N-terminal moiety of the incretins is the determinant of their activity, proteolytic truncation of the N-terminus by DPIV-IV inactivates incretins. See abstract, p. 830, first paragraph, and p. 833.

Therefore, it would be *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to use inhibitors of DP-IV to lower elevated blood glucose, because one would expect that inhibition of DP-IV would prevent this enzyme from inactivation of incretins, and thus sustain the ability of an organism to secrete insulin in response to elevation in glucose level. Further, as elevated level of glucose may trigger elevation in blood pressure (see, e.g., Barbagallo et al), it would be obvious to use DP-IV inhibitors not only to normalize glucose level, but also to normalize blood pressure level which might have been elevated due to the increase in the glucose level.

Further, Deacon et al teaches that exogenous incretins are rapidly degraded by DP-IV when administered to type 2 diabetes patients, and therefore there

intended effect of normalizing blood glucose level is short lived. The authors suggest that "inhibition of DP-IV may prove useful in the management of type 2 diabetes". Therefore, an artisan would be motivated to use inhibitors of DP-IV not only to preserve the integrity of endogenous incretins, but also to sustain the lifetime of exogenous incretins administered to diabetes patients to normalize their glucose level.

11. Claims 1,7,8 are rejected under 35 U.S.C.103(a) as obvious over Kieffer et al. (reference CAH, IDS filed 05/12/2003) alone or in combination with Deacon et al. and further in view of Barbagallo et al.

The instant claims are drawn to method for lowering elevated blood glucose by administering an effector of Dipeptidyl Peptidase (DP-IV).

Kieffer et al, as Mentlein et al discussed above, teach that incretins stimulate insulin secretion in the presence of elevated blood glucose. Further, the reference demonstrates that DP-IV is a primary enzyme involved in the degradation of incretins *in vivo* and that a specific DP-IV inhibitor reduces this inactivation of incretins.

The difference of the referenced method is that it shows the effect of the DP-IV inhibitor *in vitro*, whereas the instant invention is drawn to *in vivo* administration. It would be *prima facie* obvious to one skilled in the art at the time the invention was made to apply *in vitro* findings of Kieffer et al. for *in vivo* treatment because reduction of elevated glucose level is a desired therapeutical effect and one would have reasonable expectations, in the absence of evidence to the contrary that the *in vitro* effect, observed by Kieffer in an adequate model, will be similarly reproduced in *in vivo* conditions. Further, Deacon et al, discussed in

the previous rejection, suggest *in vivo* administration of DP-IV inhibitors to preserve *in vivo* lifetime of incretins administered to diabetes patients to reduce their blood glucose. In addition, as elevated level of glucose may trigger elevation in blood pressure (see, e.g., Barbagallo et al), it would be obvious to use DP-IV inhibitors not only to normalize glucose level, but also to normalize blood pressure level which might have been elevated due to the increase in the glucose level. Further, Deacon et al, discussed in the previous rejection, suggest *in vivo* administration of DP-IV inhibitors to preserve *in vivo* lifetime of incretins administered to diabetes patients to reduce their blood glucose.

12. Claims 1,7,8 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C.103(a) as obvious over Jenkins et al, or Powers et al, or Bachovchin et al (US Patent 5,939,560 5,462,928 (reference AM, IDS filed 05/12/2003), 5,543,396 5,462,928 (reference AJ, IDS filed 05/12/2003) and 5,462,928 (reference AH IDS filed 05/12/2003), respectively).

The referenced patents teach administration of DP-IV inhibitors . See US Patent 5,939,560, claim 7, 5,543,396, claim 6, and 5,462,928, claim 8. Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02. In the instant case, it is well known in the prior art that DP-IV is a primary enzyme involved in the degradation of incretins *in vivo,* that specific DP-IV inhibitors reduce this inactivation of incretins, and thus maintain the ability of the organism to reduce

elevation in glucose level. Further, as increase in glucose level may cause increase in blood pressure, and, conversely, decrease in glucose level may decrease blood pressure (see Barbagallo et al reference discussed above), reduction in glucose level caused by incretins will inherently cause decrease in blood pressure as well. Therefore, inhibitors of DP-IV when administered would inherently be able to preserve the activity of incretins, and thus the sustain the ability of an organism to secrete insulin in response to elevation in glucose level, and cause decrease in glucose and blood pressure levels. Further, it would be *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to use inhibitors of DP-IV to lower elevated blood glucose and blood pressure, because one would expect that inhibition of DP-IV would prevent this enzyme from inactivation of incretins, and thus sustain the ability of an organism to secrete insulin in response to elevation in glucose level.

13. Claims 1,7,8 are rejected under 35 U.S.C. 102(e) as anticipated Edmondson et al (US Patent 6699871).

Edmondson et al teach that DP IV inhibitor have utility in treating of both hyperglycemia and hypertension (see paragraph bridging columns 11 and 12). Hence, decreasing elevated level of glucose will also cause lowering in blood pressure which might have been elevated due to the increase in the glucose level.

Conclusion.

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0549.

MICHAEL BORIN, PH.D
PRIMARY EXAMINER